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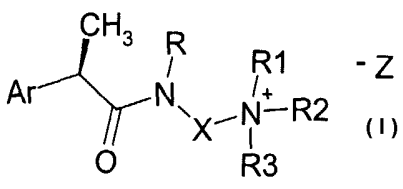
(54) Title: QUATERNARY AMMONIUM SALTS OF OMEGA-AMINOALKYLAMIDES OF R-2-ARYL-PROPIONIC ACIDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



(I)

(57) Abstract: (R)-Enantiomers of quaternary ammonium salts of general formula (I) are described: (I) where R, R_1, R_2, R_3, X and Z are as defined in the description. The process for their preparation and pharmaceutical preparations thereof are also described. The quaternary salts of the invention are useful in the inhibition of chemotaxis of neutrophils and monocytes induced by the fraction C5a of the complement and are used in the treatment of psoriasis, pemphigus and pemphigoid, rheumatoid arthritis, intestinal chronic inflammatory pathologies including ulcerative colitis, acute respiratory distress syndrome, idiopathic fibrosis, cystic fibrosis, chronic obstructive pulmonary disease and glomerulonephritis. The compounds of the invention are advantageously used in the prevention and the treatment of injury caused by ischemia and reperfusion.

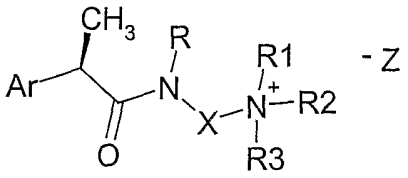
"QUATERNARY AMMONIUM SALTS OF OMEGA-AMINOALKYLAMIDES OF R-2-ARYL-PROPIONIC ACIDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"

Introduction and background of the invention

The present invention relates to compounds useful in the inhibition of the chemotactic activation induced by the fraction C5a of complement and from other chemotactic proteins (chemokines) that exert their action by activating a 7-transmembrane-domain (7-TM) receptor. Said compounds are quaternary ammonium salts of R-2-arylpropionamides useful in the treatment of pathologies depending on the chemotactic activation of neutrophils and monocytes induced by the fraction C5a of the complement. In particular, the compounds of the invention are useful in the treatment of psoriasis, rheumatoid arthritis, ulcerative colitis, acute respiratory distress syndrome, idiopathic fibrosis, glomerulonephritis and in the prevention of injury caused by ischemia and reperfusion.

Detailed description of the invention

The present invention relates to (R)-2-aryl-propionamides of formula (I):



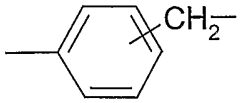
(I)

wherein

- Ar represents a substituted or non-substituted aryl group;
- R represents hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, optionally substituted by a CO_2R_4 group, wherein R_4 represents hydrogen or a linear or branched C_1-C_6 alkyl group or a linear or branched C_2-C_6 alkenyl group;
- X represents:

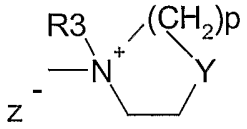
linear or branched C_1-C_6 alkylene, C_4-C_6 alkenylene, C_4-C_6 alkynylene, optionally substituted by a CO_2R_4 group or by a $CONHR_5$ group wherein R_5 represents hydrogen, linear or branched C_2-C_6 alkyl or an OR_4 group, R_4 being defined as above;

- phenyl or a phenylmethylene group of formula:



- a $(CH_2)_m$-B-$(CH_2)_n$, group, optionally substituted by a CO_2R_4 or $CONHR_5$ group, as defined above, wherein B is an oxygen or sulfur atom, m is zero or an integer from 2 to 3 and n is an integer from 2 to 3; or B is a CO, SO or CONH group, m is an integer from 1 to 3 and n is an integer from 2 to 3;
- or X together with the nitrogen atom to which it is bound and with the R_1 group forms a nitrogen containing 3-7 membered heterocyclic monocyclic or polycyclic ring;
- R_1, R_2 and R_3 are independently linear or branched C_1-C_6 alkyl, optionally substituted by an oxygen or sulfur atom, a C_3-C_7 cycloalkyl, C_3-C_6 alkenyl, C_3-C_6-alkynyl, aryl, aryl-C_1-C_3-alkyl, hydroxy-C_2-C_3-alkyl group;

or R_1 and R_2 together with the N atom to which they are bound, form a nitrogen containing 3-7 membered heterocyclic ring of formula (II) and R3 independently has the meanings as defined above.



(II)

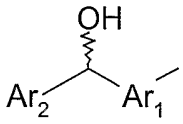
In the general formula (II)

- Y represents a single bond, a methylene group, an oxygen atom, a nitrogen atom or a sulfur atom
- p represents an integer from 0 to 3;
- Z represents conventional anions used as counter-ions of quaternary ammonium salts which are pharmaceutically acceptable, such as, for example, halide ions Cl^-, I^-, Br^-, the sulfate anion or anions derived from sulfonic acids such as methansulfonate or p-toluensulfonate.

In the compounds of general formula (I), the aryl group Ar is preferably chosen among:

a) an Ar_a mono- or poly-substituted aryl group, of the most common (±) 2-aryl-propionic acids in current therapeutic use: alminoprofen, benoxaprofen, carprofen, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, loxoprofen, R-naproxen, pirprofen and its dehydro and dihydro derivatives, pranoprofen, surprofen, tiaprofenic acid, zaltoprofen;

b) an aryl-hydroxymethyl-aryl group of formula (IIIa) both as diastereoisomer mixture, or as single diastereoisomers,



(IIIa)

wherein, when Ar_2 is phenyl Ar_1 is selected from the group consisting of phenyl and thien-2-yl while when Ar_1 is phenyl, Ar_2 is selected from the group consisting of phenyl, 4-thienyl, pyridyl.

c) an aryl of formula (IIIb):

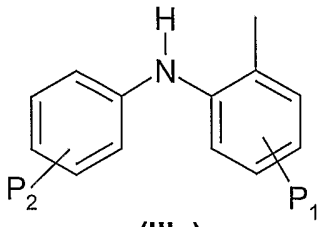
$$\Phi-Ar_b$$

(IIIb)

wherein:

- Ar_b is a phenyl mono- or poly-substituted by hydroxy, mercapto, C_1-C_3-alcoxy, C_1-C_3-alkylthio, chlorine, fluorine, trifluoromethyl, nitro, amino, optionally substituted C_1-C_7-acylamino;
- Φ is hydrogen; a linear or branched C_1-C_5 alkyl, C_2-C_5- alkenyl or C_2-C_5-alkynyl residue optionally substituted by C_1-C_3-alkoxycarbonyl, substituted or non-substituted phenyl, 2-, 3- or 4-pyridyl, quinolin-2-yl; a C_3-C_6-cycloalkyl; 2-furyl; 3-tetrahydrofuryl; 2-thiophenyl; 2-tetrahydrothiophenyl or a C_1-C_8-(alkanoyl, cycloalkanoyl, arylalkanoyl)-C_1-C_5- alkylamino group e.g. acetyl-N-methyl-amino, pivaloyl-N-ethyl-amino;

d) a 2-(phenylamino)-phenyl of formula (III c):



(IIIc)

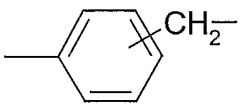
wherein the substituents P_1 and P_2 indicate that the two phenyl groups bear, each independently, mono- or poly-substitutions with C_1-C_4-alkyl, C_1-C_3-alcoxy groups, chlorine, fluorine and/or trifluoromethyl.

Preferred compounds according to the invention are those wherein:

R is hydrogen;

X is:

- a linear C_1-C_6 alkylene, preferably C_2-C_4, optionally substituted at C_1 by a -CO_2R_4 group as defined above;
- a linear C_1-C_6 alkylene optionally substituted at C_1 by a -$CONHR_5$ group wherein R_5 is OH;
- 2-butynylene, cis-2-butenylene, trans-2-butenylene;
- 3-oxa-pentylene, 3-thio-pentylene, 3-oxa-hexylene, 3-thio-hexylene;
- $(CH_2)_m$-CO-NH-$(CH_2)_n$-wherein m and n are each independently an integer from 2 to 3;
- (CHR')-CONH-($CH_2)_n$ wherein n is an integer from 2 to 3 and R' is a methyl, having absolute configuration R or S;
- a phenyl or phenylmethylene group of formula:



- or X, together with the N atom, form an azocycloaliphatic ring, preferably 1-methyl-piperidin-4-yl or 1,5-tropan-3-yl;

Preferred compounds are, in addition, those wherein the $NR_1R_2R_3$ group represents a trimethylammonium, triethylammonium, N-methyl-N,N-diethylammonium, N-methyl-N,N-diisopropylammonium, N-cyclohexylmethyl-N,N-dimethylammonium, N-cyclopentylamino-N,N-dimethylammonium, N-methyl-1-

piperidinium, N-ethyl-1-piperidinium, N-methyl-4-morpholinium, N-methyl-4 thiomorpholinium, N-benzyl-N,N-dimethylammonium, N-allyl-1-piperidinium, 4-oxy-N-methyl-piperidinium group.

Examples of particularly preferred aryl groups comprise:

4-isobutylphenyl, 4-cyclohexylmethylphenyl, 4-(2-methyl)allyl-phenyl, 3-phenoxyphenyl, 3-benzoyl-phenyl, 3-acetyl-phenyl, the single (R) (S) diastereoisomers and the diastereoisomeric (R,S) mixture of 3-C_6H_5-CH(OH)-phenyl, 3-CH_3-CH(OH)-phenyl, 5-C_6H_5-CH(OH)-thienyl, 4-thienyl-CH(OH)-phenyl, 3-(pyrid-3-yl)-CH(OH)-phenyl, 5-benzoyl-thien-2-yl, 4-thienoyl-phenyl, 3-nicotinoyl-phenyl, 2-fluoro-4-phenyl, 6-metoxy-2-naphthyl, 5-benzoyl-2-acetoxy-phenyl, 5-benzoyl-2-hydroxy-phenyl, 4-cyclopentyl-phenyl, 4-(2-oxo-cyclopentyl)-phenyl, 4-(2-oxo-cyclohexyl)-phenyl.

Particularly preferred aryl groups of formula (III b) are phenyl groups 3-substituted by: isoprop-1-en-1-yl, isopropyl, pent-2-en-3-yl; pent-3-yl; 1-phenylethylen-1-yl; α-methylbenzyl.

Particularly preferred aryls of formula (III c) are: 2-(2,6-dichloro-phenyl-amino)-phenyl; 2-(2,6-dichloro-phenyl-amino)-5-chloro-phenyl; 2-(2,6-dichloro-3-methyl-phenyl-amino)-phenyl; 2-(3-trifluoromethyl-phenyl-amino)-phenyl.

Examples of P_2 substituted phenyl groups comprise phenyl groups substituted by one to three halogen atoms, C_1-C_4 alkyl groups, methoxy, trifluoromethyl, nitro, cyano, haloalkoxy.

Particularly preferred compounds of the invention are:

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-trimethylammonium iodide;

(R)-{3-[2-(3-benzoylphenyl)-propionylamino] propyl}-trimethylammonium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl} -N-ethyl-N,N-dimethylammonium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-N-cyclohexylmethyl- N,N-dimethylammonium iodide;

(R)-{3-[2-(4-cyclopentylmethylphenyl)-propionylamino] propyl}-trimethylammonium iodide;

(R)-{3-[2-(3-benzoylphenyl)-propionylamino] propyl}-N-isopropyl-N,N-dimethylammonium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] butyl-trimethylammonium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-1-methyl-piperidinium iodide;

(R)-{3-[2-(3-benzoylphenyl)-propionylamino] propyl}-1-methyl piperidinium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-4-methyl-morpholinium iodide;

(R)-{3-[2-(3-isopropylphenyl)-propionylamino] propyl}-4-methyl-thiomorpholinium methanesulfonate;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] ethyl-trimethylammonium bromide;

(R)-2-[(4-isobutylphenyl)-propionylamino]-1,1-dimethyl)piperidinium p-toluenesulfonate;

(R),(S')-2-(4-isobutylphenyl)-N-[(1-carboxy-2"-N,N,N-trimethylammonium)ethyl] propionamide methanesulfonate;

R(-)-2-[(4-isobutylphenyl)-N-(trimethylammoniumethyl) methylamide] propionamide iodide;

(R)(3-{2-[2(2,6-dichlorophenylamino)-phenyl]-propionylamino}-propyl)-trimethylammonium methanesulfonate;

(2R), (4"S)1-{4-carboxy-4-[2-(4-isobutyl-phenyl)-propionylamino] butyl}-1-methyl-piperidinium iodide;

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(N-benzyl)-N,N-dimethylammonium iodide;

2R-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(1"methyl-4" carboxyamide) piperidinium iodide;

(2R)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(1"-methyl-4" carbonyl) piperidinium iodide;

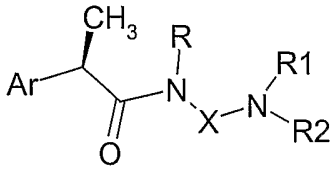
R(-)-{3,-[-(4'-isobutylphenyl)-propionylamino]-propyl}-triethylammonium iodide;

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-1-allylpiperidinium bromide;

R(-)-2-[(4'-isobutyl)phenyl]-N-[4"-N,N,N-trimethylaminophenyl] propionamide iodide;

R(-)-2-[(4'-isobutyl)phenyl]-N-[4"-N,N,N-trimethylaminomethylphenyl] propionamide iodide.

Known methods for the alkylation of tertiary amine groups (Menschutkin reaction) are used for the preparation of formula (I) compounds; compounds of formula (IV), wherein Ar, R, R_1, R_2 and X are as above defined, are reacted with compounds of formula R_3Z where R_3 is defined as above and Z is a conventional leaving group such as chloride, bromide, iodide, methanesulfonate, p-toluensulfonate or sulfate.



(IV)

The alkylation reactions are normally conducted at room temperature, using conventional protic or aprotic preferably anhydrous solvents or their mixtures, optionally in the presence of a strong non-nucleophilic base. Alternatively, some of compounds of formula (I) can be obtained starting from compounds of formula (IV) by reaction with Michael-type unsaturated substrates catalyzed by mineral acids such as HCl or HNO_3.

The preparation of compounds of formula (IV) is described in International Patent Application PCT/EP02/01974. Some of the compounds of formula (IV) are new with respect to specific compounds described in the above patent application, and were prepared with the methods described further below in the Preparations section.

It is understood that is the synthesis of compounds formula (I) starting from the amides of formula (IV) wherein substituents R_1 and R_2 can be -H independently is included in the process. If desired, the primary and secondary amines can be reacted in the conditions of exhaustive alkylation with compounds of formula R_3Z to yield the compounds of the invention of formula (I) wherein at least two of the

residues defined as R_1, R_2 and R_3 are the same. The reaction is carried out under the same conditions as described for the conversion of the amides of formula (IV) into the compounds of the invention of formula (I).

Alternatively, the primary or secondary amides of formula (IV) can be converted into formula (I) compounds in two consecutive steps. In the first step of mono-or dialkylation, the reaction is carried out at room temperature or by heating in the presence of one or two equivalents of R_2Z alkylating agent, depending on the degree of substitution of the starting amine group. The reactions are carried out in conventional protic or aprotic preferably anhydrous solvents or their mixtures, optionally in the presence of a strong non-nucleophilic base.

The compounds of the invention of formula (I) were evaluated *in vitro* for their ability to inhibit chemotaxis of polymorphonucleate leukocytes (hereinafter referred to as PMNs) and monocytes induced by the fractions of the complement C5a and C5a-desArg. For this purpose, to isolate the PMNs from heparinized human blood, taken from healthy adult volunteers, mononucleates were removed by means of sedimentation on dextran (according to the procedure disclosed by W.J. Ming *et al.*, J. Immunol., 138, 1469, 1987) and red blood cells by a hypotonic solution. The cell vitality was calculated by exclusion with Trypan blue, whilst the ratio of the circulating polymorphonucleates was estimated on the cytocentrifugate after staining with Diff Quick.

Human recombinant fractions C5a and C5a-desArg (Sigma) were used as stimulating agents in the chemotaxis experiments, giving practically identical results.

The lyophilized C5a was dissolved in a volume of HBSS containing 0.2% bovin serum albumin BSA so thus to obtain a stock solution having a concentration of 10^{-5} M to be diluted in HBSS to a concentration of 10^{-9} M , for the chemotaxis assays.

In the chemotaxis experiments, the PMNs were incubated with the compounds of the invention of formula (I) for 15' at 37°C in an atmosphere containing 5% CO_2.

The chemotactic activity of the C5a was evaluated on human circulating polymorphonucleates (PMNs) resuspended in HBSS at a concentration of $1.5x10^6$ PMNs per mL.

During the chemotaxis assay (according to W. Falket et al., J. Immunol. Methods, 33, 239, 1980) PVP-free filters with a porosity of 5 μm and microchambers suitable for replication were used.

The compounds of the invention in formula (I) were evaluated at a concentration ranging between 10^{-6} and 10^{-10} M; for this purpose they were added, at the same concentration, both to the lower pores and the upper pores of the microchamber. The wells in the lower part contain the solution of C5a or the simple carrier, those in the upper part contain the suspension of PMNs.

Inhibition of C5a-induced chemotactic activity by the individual compounds of the invention of formula (I) was evaluated by incubating the microchamber for the chemotaxis for 60 min at 37°C in an atmosphere containing 5% CO2.

Evaluation of the ability of the compounds of the invention of formula (I) to inhibit C5a-induced chemotaxis of human monocytes was carried out according to the method disclosed by Van Damme J. et al. (Eur. J. Immunol., 19, 2367, 1989). Inhibition of C5a-induced chemotactic activity by the individual compounds of the invention of formula (I) towards human monocytes was evaluated at a concentration ranging between 10^{-6} and 10^{-10} M by incubating the microchamber for the chemotaxis for 120 min. at 37°C in an atmosphere containing 5% CO2.

By way of example, the inhibition data of the chemotaxis of PMN ($C=10^{-6}$ M) of some representative compounds of the invention are reported in the following table:

COMPOUND	% INHIBITION ($C=10^{-6}$ M)
(R)-(3-{2-[2-(2,6-dielorophenylamino)-phenyl]-propionylamino}-propyl)-trimethylammonium iodide	62±3
R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-trimethylammonium iodide	53±6

R(-)-2-[(4'-isobutylphenyl)-propionylamino]-1,1-dimethylpiperidinium iodide	18±9
R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-1-methyl-piperidinium iodide	24±4
R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-N-cyclohexylmethyl-propyl}N,N-dimethyl-ammonium methanesulfonate	57±4
R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(N-benzyil)-N,N-dimethylammonium iodide	22±4

The compounds of formula (I), evaluated *ex vivo* in the blood *in toto* according to the procedure disclosed by Patrignani et al., in J. Pharmacol. Exper. Ther., 271, 1705, 1994, were found to be totally ineffective as inhibitors of cyclooxygenase (COX) enzymes.

In almost all cases, the compounds of formula (I) do not interfere with the production of PGE_2 induced in murine macrophages by lipopolysaccharides stimulation (LPS, 1 μg/mL) at a concentration ranging between 10^{-5} and 10^{-7} M. Inhibition of the production of PGE_2 which may be recorded, is mostly at the limit of statistical significance, and more often is below 15-20% of the basal value.

It is therefore a further object of the present invention the use of the compounds of the invention as medicaments.

In view of the experimental evidence discussed above and of the role performed by the complement cascade, and namely its fraction C5a, in the processes that involve the activation and the infiltration of neutrophils, the compounds of the invention are particularly useful in the treatment of diseases such as psoriasis (R. J. Nicholoff et al., Am. J. Pathol., 138, 129, 1991), pemphigo and pemphigoid, rheumatoid arthritis (M. Selz et al., J. Clin. Invest., 87, 463, 1981), intestinal chronic inflammatory pathologies such as ulcerative colitis (Y. R. Mahida et al., Clin. Sci., 82, 273, 1992), acute respiratory distress syndrome and idiopathic fibrosis (E. J. Miller, previously cited, and P. C. Carré et al., J. Clin. Invest., 88, 1882, 1991), cystic fibrosis, chronic obstructive pulmonary disease, glomerulonephritis (T. Wada et al.,

J. Exp. Med., 180, 1135, 1994) and in the prevention and the treatment of injury caused by ischemia and reperfusion.

The compounds of formula (IV) for their use as medicaments are described in International Patent Application PCT/EP02/01974. The new amides of formula (IV) described below in the Preparations section have biological activity comparable to that of amides described in the above patent application and can be used for the treatment of the same pathologies.

To this purpose, the compounds of the invention of formula (I) conveniently are formulated in pharmaceutical compositions using conventional techniques and excipients such as those described in "Remington' s Pharmaceutical Sciences Handbook" MACK Publishing, New York, 18th ed., 1990.

The compounds of the invention can be administered by intravenous injection, as a bolus, in dermatological preparations (creams, lotions, sprays and ointments), by inhalation as well as orally in the form of capsules, tablets, syrup, controlled- release formulations and the like.

The average daily dose depends on several factors such as the severity of the disease, the condition, age, sex and weight of the patient. The dose will vary generally from 1 to 1500 mg of compounds of formula (I) per day, optionally divided in multiple administrations. Higher doses can be administered for long periods of time, thanks to the low toxicity of compounds of the invention.

The following examples and preparations serve to illustrate the invention.

By convention, apices (e.g. R', S', S" etc.) show the absolute configurations present in substituent R_1 in the compounds of the invention of formula (I).

Abbreviations: THF: tetrahydrofuran; DMF: dimethylformamide; EtAc: ethyl acetate, HOBZ: hydroxybenzotriazol, DCC:dicyclohexylcarbodiimide.

Materials and methods

The amines used as reagents in the synthesis of compounds of formula (IV) are known products, generally commercially available or they can be prepared according to methods described in the literature.

The synthesis of 2-aryl-propionic acids of formula ϕ-Ar_3-$C(CH_3)H$-CO_2H and of their R-enantiomers is reported in International patent application PCT/EP01/01285.

The optical resolution was carried out by means of salification with R(+)-N-methylbenzylamine according to the method described by Akguen et al,. Arzneim. Forsch., 46:9 891-894, 1996.

PREPARATIONS

Preparation of Omega-aminoalkylamides of R-2-arylpropionic acid as intermediates

The preparation of compounds of formula (IV) is disclosed in International Patent application PCT/EP02/01974. Some compounds of formula (IV) are new and described for the first time in the present patent application.

Examples of the preparation of the new amides of formula (IV) are reported below.

PREPARATION 1

R(-)-2-[(3-benzoyl)phenyl]-N-[3"-(N',N'-dimethylamino)propyl]propionamide

Hydroxybenzotriazol (0.604 g, 3.93 mmol) and N,N-dicyclohexylcarbodiimmide (0.81 g, 3.93 mmol) are added to a solution of R(-)-ketoprofen (lg, 3.93 mmol) in anhydrous dichloromethane (25 mL). The mixture is stirred at r.t. for 30 min; N,N-dimethyl-1,3-propandiamine (0.49 mL, 3.93 mmol) is added to the suspension formed. The resulting suspension is stirred at r.t. overnight. Dicyclohexylurea (DCU) is then filtered off under vacuum and the filtrate is evaporated at reduced pressure; the crude oily residue is taken up in acetonitrile (20 mL) and the mixture left overnight at T=4°C. After the filtration of a further aliquot of DCU, the filtrate is again evaporated at reduced pressure and the residue is purified by means of flash chromatography on silica gel (eluent $CHCl_3/CH_3OH$ 8:2); R(-)-2-[(3'-benzoyl)phenyl]-N-[3"-(N',N'-dimethylamino)propyl]-propionamide (0.997 g, 2.94 mmol) is obtained as a transparent oil.

Yield 75%

$[\alpha]_D$ = -20 (c = 0.9; CH_3OH)

^{1}H-NMR ($CDCl_3$) δ 7.90-7.40 (m, 9H); 7.25 (s, 1H, CONH); 3.65 (m, 1H); 3.36 (m, 2H); 2.38 (m, 2H); 2.20 (s, 6H); 1.62 (m, 5H).

In a similar way the following compounds were also prepared:

R(-)-2-[(3'-benzoyl)phenyl]-N-(3"-N"'-piperidinopropyl)-propionamide

Yield 80%

$[\alpha]_D$ = -47.5 (c = 0.3; CH_3OH)

^{1}H-NMR ($CDCl_3$) δ 7.85-7.42 (m, 9H + CONH); 3.80 (m, 1H); 3.57-3.28 (m, 4H); 2.85 (m, 2H); 2.10 (m, 2H); 1.65 (m, 11H).

R(-)-2-[(4'-isobutyl)phenyl]-N-[3"-N'-(4",4"-piperidinediol)-propyl]-propionamide

$[\alpha]_D$ = -19.5 (c = 1; CH_3OH)

^{1}H-NMR (DMSO-d6) δ 8.05 (t, 1H, J= 6Hz, CONH); 7.25 (d, 2H, J=8Hz); 7.08 (d, 2H, J=8Hz); 3.55 (m, 1H); 3.40 (m, 2H); 3.35-3.25 (m, 6H); 2.38 (d, 2H, J=7Hz); 2.05 (m, 4H); 1.85 (m, 1H); 1.50 (m, 2H); 1.35 (d, 3H, J=7Hz); 0.87 (d, 6H, J=7Hz).

R(-)-2-[(4'-isobutyl)phenyl]-N-[3"-N'-(4"-carboxyamidopiperidin)-propyl]propionamide

$[\alpha]_D$ = -28.5 (c = 1; CH_3OH)

^{1}H-NMR (DMSO-d6) δ 8.45 (d, 2H, J=8Hz), CONH2); 8.10 (t, 1H, J= 6Hz, CONH); 7.35 (d, 2H, J=8Hz); 7.20 (d, 2H, J=8Hz); 3.65 (m, 1H); 3.42 (m, 2H); 3.15-2.90 (m, 6H); 2.35 (d, 2H, J=7Hz); 2.15 (m, 1H); 1.80 (m, 1H); 1.55 (m, 6H); 1.35 (d, 3H, J=7Hz); 0.85 (d, 6H, J=7Hz).

R(-)-2-[(4'-isobutyl)phenyl]-N-[4"-N,N-dimethylaminomethylphenyl]-propionamide

$[\alpha]_D$ = -35 (c=1; CH_3OH)

^{1}H-NMR ($CDCl_3$): δ 7.82 (dd, 1H, J_1=8.4Hz, J_2=2Hz); 7.55 (d, 1H, J=2Hz); 7.20 (m, 2H); 7.10 (m, 2H); 6.85 (d, 2H, J=8.4Hz); 6.15 (bs, 1H, CONH); 3.70 (s, 2H); 3.50 (m, 1H); 3.20 (s, 6H); 2.45 (d, 2H, J=7Hz); 1.88 (m, 1H); 1.50 (d, 3H, J=7Hz); 0.85 (d, 6H, J=7Hz).

EXAMPLES

QUATERNARY SALTS OF OMEGA-AMINOALKYLAMIDES OF R-2-ARYL-PROPIONIC ACIDS

Example 1

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-1-methyl-piperidinium iodide

R(-)-2-[(4' -isobutyl)phenyl]-N-[3"-N' -(N' -methyl)piperidinopropyl]-propionamide (0.095 g; 0.287 mmol) is dissolved in anhydrous tetrahydrofuran (6 mL) under inert atmosphere. Methyl iodide (0.1mL, 1.61 mmol) is added to the solution; the solution is stirred at r.t. for 18 hours until the starting reagent is no longer detectable. The solvent is then evaporated at reduced pressure and the residue is taken up in isopropyl ether. A white precipitate forms which is stirred for 6 hours. The precipitate is filtered and dried under vacuum at T=40°C to yield the R(-)-2-[(4'-isobutyl)phenyl]-N-[3"-N' -(N'-methyl)-piperidinopropyl] propionamide iodide (0.114 g; 0.24 mmol) as a clear yellow waxy solid.

Yield 84%

$[\alpha]_D$ = -12 (c = 0.7; CH_3OH)

^{1}H-NMR (DMSO-d_6) δ 8.05 (t, 1H, J= 6Hz, CONH); 7.25 (d, 2H, J=8Hz); 7.08 (d, 2H, J=8Hz); 3.55 (m, 1H); 3.25-3.02 (m, 8H); 2.90 (s, 3H); 2.38 (d, 2H, J=7Hz); 1.85-1.55 (m, 7H); 1.50 (m, 2H); 1.35 (d, 3H, J=7Hz); 0.88 (d, 6H, J=7Hz).

The following compounds were prepared by using the method reported above:

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-trimetilammonium iodide

m.p. 105-110°C

$[\alpha]_D$ = -17 (c = 1.0; CH_3OH)

^{1}H-NMR ($CDCl_3$) δ 7.42 (d, 2H, J=8Hz); 7.20 (t, 1H, J=6Hz, CONH); 7.07 (d, 2H, J=8Hz); 3.83 (m, 1H); 3.77 (m, 2H); 3.55-3.20 (m, 2H); 3.18 (s, 9H); 2.40 (d, 2H, J=7Hz); 2.05 (m, 2H); 1.83 (m, 1H); 1.45 (d, 3H, J=7Hz); 0.9 (d, 6H, J=7Hz).

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-butyl}-trimethylammonium iodide

m.p. 100-103°C

$[\alpha]_D$ = -25 (c = 1.0; CH_3OH)

^{1}H-NMR ($CDCl_3$) δ 7.25 (d, 2H, J=8Hz); 7.09 (d, 2H, J=8Hz); 6.18 (s, 1H, CONH); 3.61 (m, 1H); 3.28 (m, 2H); 3.12 (m, 2H); 3.08 (s, 9H); 2.44 (d, 2H, J=7Hz); 1.81 (m, 1H); 1.75 (m, 4H); 1.50 (d, 3H, J=7Hz); 0.88 (d, 6H, J=7Hz).

R(-)-2-[(4'-isobutylphenyl)-propionylamino]-l,l-dimethylpiperidinium iodide

m.p. 80-85°C

$[\alpha]_D$ = -7 (c = 1.2; CH_3OH)

^{1}H-NMR (DMSO-d_6) δ 7.91 (d, 1H, J=7Hz, CONH); 7.22 (d, 2H, J=8Hz); 7.08 (d, 2H, J=8Hz); 3.80 (m, 1H); 3.53 (m, 1H); 3.35-3.30 (m, 4H); 3.08 (s, 3H); 3.00 (s, 3H); 2.40 (d, 2H, J=7Hz); 1.95-1.65 (m, 5H); 1.3 (d, 3H, J=7Hz); 0.87 (d, 6H, J=7Hz).

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-4-methylmorpholinium iodide

m.p. 84-87°C

$[\alpha]_D$ = -17 (c = 0.5; CH3OH)

1H-NMR ($CDCl_3$) δ 7.45 (d, 2H, J=8Hz); 7.02 (m, 3H, CONH + 2Har.); 4.25 (m, 2H); 3.92 (m, 1H); 3.88 (m, 1H); 3.80 (m, 1H); 3.53 (m, 1H); 3.35 (m, 2H); 3.15 (m, 1H); 3.00 (s, 3H); 2.92-2.70 (m, 4H); 2.40 (d, 2H, J=7Hz); 2.15 (m, 2H); 1.88 (m, 1H); 1.45 (d, 3H, J=7Hz); 0.92 (d, 6H, J=7Hz).

R(-)-2-[(4'-isobutylphenyl)-N-(trimethylammoniumethyl)-methylamide]-propionamide iodide

m.p. 70-72°C

$[\alpha]_D$ = -18 (c = 1.0; CH3OH)

1H-NMR (DMSO-d_6) δ 7.22 (d, 2H, J=8Hz); 7.11 (d, 2H, J=8Hz); 6.25 (bs, 2H, CONH); 3.57 (m, 1H); 3.30 (m, 2H); 3.10 (s, 9H); 2.45 (d, 2H, J=7Hz); 2.40 (m, 2H); 1.88 (m, 1H); 1.75 (m, 2H); 1.52 (d, 3H, J=7Hz); 0.92 (d, 6H, J=7Hz).

R(-)-{3-[2-(3'-benzoylphenyl)-propionylamino]-propyl}-trimethylammonium iodide

m.p. 62-65°C

$[\alpha]_D$ = -16.3 (c = 1.0; CH_3OH)

^{1}H-NMR (DMSO-d6) δ 8.20 (t, 1H, J=7Hz, CONH); 7.81-7.47 (m, 9H); 3.75 (m, 1H); 3.27-3.05 (m, 4H); 3.00 (s, 9H); 1.85 (m, 2H); 1.37 (d, 3H, J=7Hz).

R(-)-{3-[2-(3-benzoylphenyl)propionylamino]-propyl)]-1-methylpiperidinium iodide

m.p. 69-73°C

$[\alpha]_D$ = -10 (c = 0.6; CH_3OH)

^{1}H-NMR (DMSO-d_6) δ 8.18 (t, 1H, J=7Hz, CONH); 7.80-7.47 (m, 9H); 3.70 (m, 1H); 3.28-3.05 (m, 8H); 2.92 (s, 3H); 1.87-1.53 (m, 6H); 1.42 (m, 2H); 1.38 (d, 3H, J=7Hz).

(R)-{3-{2-[2-(2,6-dichlorophenylamino)-phenyl]-propionylamino}-propyl)-trimethylammonium iodide

$[\alpha]_D$ = -15 (c = 1.0; CH_3OH)

^{1}H-NMR (DMSO-d_6) δ 8.48 (m, 1H, CONH); 8.27 (s, 1H, NH); 7.52 (d, 2H, J=8Hz); 7.18 (q, 2H, J1=8Hz, J2=16Hz); 7.05 (t, 1H, J=7Hz); 6.88 (t, 1H, J=7Hz); 6.30 (d, 1H, J=8Hz); 3.75 (m, 1H); 3.30 (m, 11H); 3.21 (m, 2H); 1.88 (m, 2H); 1.64 (d, 3H, J=7Hz).

(2R), (4"S) 1-{4-carboxy-4-[2-(4-isobutyl-phenyl)-propionylamino]-butyl}-1-methyl-piperidinium iodide

$[\alpha]_D$ = -9.5 (c=1.0; CH_3OH)

^{1}H-NMR (DMSO-d_6): δ 8.66 (bs, 1H, CONH); 7.22 (d, 2H, J=8Hz); 7.5 (d, 2H, J=8Hz); 4.00 (m, 1H); 3.80 (m, 1H); 2.95 (m, 6H); 2.90 (s, 3H); 2.45 (d, 2H, J=7Hz); 1.82 (m, 1H); 1.70-1.33 (m, 10H); 1.31 (d, 3H, J=7Hz); 0.89 (d, 6H, J=7Hz).

(2R)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(1"-methyl-4"carbonyl)-piperidinium iodide

$[\alpha]_D$ = -39 (c = 1; CH_3OH)

^{1}H-NMR (DMSO-d6) δ 8.15 (t, 1H, J= 6Hz, CONH); 7.28 (d, 2H, J=8Hz); 7.12 (d, 2H, J=8Hz); 3.80 (m, 1H); 3.70 (m, 2H); 3.35-3.25 (m, 6H); 3.18 (s, 3H); 2.35 (d, 2H, J=7Hz); 2.12 (m, 4H); 1.85 (m, 1H); 1.50 (m, 2H); 1.37 (d, 3H, J=7Hz); 0.87 (d, 6H, J=7Hz).

2R-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(1"-methyl-4"-carboxyamide)-piperidinium iodide

$[\alpha]_D$ = -25 (c = 1; CH_3OH)

^{1}H-NMR (DMSO-d6) δ 8.74 (d, 2H, J=8Hz, CONH2); 8.18 (t, 1H, J= 6Hz, CONH); 7.30 (d, 2H, J=8Hz); 7.22 (d, 2H, J=8Hz); 3.75 (m, 1H); 3.45 (m, 2H); 3.35 (s, 3H); 3.20-3.00 (m, 6H); 2.38 (d, 2H, J=7Hz); 2.15 (m, 1H); 1.90 (m, 1H); 1.75 (m, 6H); 1.35 (d, 3H, J=7Hz); 0.85 (d, 6H, J=7Hz).

R(-)-2-[(4'-isobutyl)-phenyl]-N-[4"-N,N,N-trimethylaminomethylphenyl]-propionamide iodide

$[\alpha]_D$ = -23 (c=1; CH_3OH)

^{1}H-NMR (DMSO-d_6): δ 7.80 (dd, 1H, J_1=8.4Hz, J_2=2Hz); 7.55 (d, 1H, J=2Hz); 7.24 (m, 2H); 7.10 (m, 2H); 7.00 (d, 2H, J=8.4Hz); 6.20 (bs, 1H, CONH); 3.70 (s, 2H); 3.50 (m, 1H); 3.20 (s, 9H); 2.45 (d, 2H, J=7Hz); 1.88 (m, 1H); 1.50 (d, 3H, J=7Hz); 0.85 (d, 6H, J=7Hz).

Example 2

The following compound was prepared according to the method described in Example 1, but using ethyliodide as the reagent:

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl} triethylammonium iodide

m.p. 100-102°C

$[\alpha]_D$ = -19.5 (c = 1.0; CH_3OH)

^{1}H-NMR ($CDCl_3$) δ 7.43 (d, 2H, J=8Hz); 7.22 (t, 1H, J=6Hz, CONH); 7.10 (d, 2H, J=8Hz); 3.83 (m, 1H); 3.77 (m, 2H); 3.55-3.35 (m, 2H); 3.15 (q, 6H, J=7Hz); 2.95 (t, 9H, J=7Hz); 2.42 (d, 2H, J=7Hz); 2.05 (m, 2H); 1.85 (m, 1H); 1.45 (d, 3H, J=7Hz); 0.9 (d, 6H, J=7Hz).

Example 3

The following compound was prepared according to the method described in Example 1, but using benzyliodide as the reagent :

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(N-benzyl)-N,N-dimethylammonium iodide

m.p. 97-100°C

$[\alpha]_D$ = -12 (c = 1.0; CH_3OH)

^{1}H-NMR ($CDCl_3$) δ 7.42 (d, 2H, J=8Hz); 7.30-7.25 (m, 5H); 7.20 (t, 1H, J=6Hz, CONH); 7.07 (d, 2H, J=8Hz); 3.85 (m, 1H); 3.72 (m, 2H); 3.68 (s, 2H); 3.55-3.32 (m, 2H); 3.20 (s, 6H); 2.40 (d, 2H, J=7Hz); 2.05 (m, 2H); 1.83 (m, 1H); 1.45 (d, 3H, J=7Hz); 0.9 (d, 6H, J=7Hz).

Example 4

The following compound was prepared according to the method described in Example 1, but using cyclohexylmethyl metanesulfonate as the reagent:

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-N-cyclohexylmethyl-N,N-dimethyl-ammonium metaneosulfonate

$[\alpha]_D$ = -23 (c = 1.0; CH_3OH)

^{1}H-NMR (DMSO-d_6) δ 7.44 (d, 2H, J=8Hz); 7.20 (t, 1H, J=6Hz, CONH); 7.08 (d, 2H, J=8Hz); 3.83 (m, 1H); 3.77 (m, 2H); 3.55-3.20 (m, 4H); 3.18 (s, 6H); 3.00 (s, 3H); 2.40 (d, 2H, J=7Hz); 2.05 (m, 2H); 1.83 (m, 1H); 1.75 (m, 5H); 1.48 (m, 1H); 1.45 (d, 3H, J=7Hz); 1.22 (m, 3H); 0.95 (m, 2H); 0.9 (d, 6H, J=7Hz).

Example 5

The following compound was prepared according to the method described in Example 1, but using allyl bromide in lieu of methyl iodide

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-1-allylpiperidinium bromide

$[\alpha]_D$ = -14.5 (c = 0.5; CH_3OH)

^{1}H-NMR (DMSO-d6) δ 8.05 (t, 1H, J= 6Hz, CONH); 7.25 (d, 2H, J=8Hz); 7.08 (d, 2H, J=8Hz); 6.05 (m, 1H); 5.35 (d, 1H, J=2Hz); 5.15 (d, 1H, J=2Hz); 3.80 (d, 2H, J=7Hz); 3.55 (m, 1H); 3.25-3.02 (m, 8H); 2.38 (d, 2H, J=7Hz); 1.85-1.55 (m, 7H); 1.50 (m, 2H); 1.35 (d, 3H, J=7Hz); 0.88 (d, 6H, J=7Hz).

Example 6

The following compound was prepared starting from the (4-aminophenyl)trimethylammonium iodide hydrochloride (commercial reagent) :

R(-)-2-[(4'-isobutyl)phenyl]-N-[4"-NNN-trimethylaminophenyl]-propionamide iodide

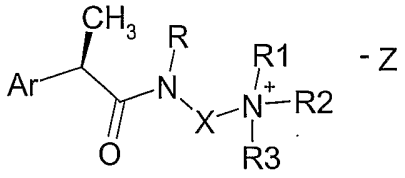
Hydroxybenzotriazol (0.62 g; 4.58 mmol) is added, at T=0°C, to a solution of (R)(-)Ibuprofen (1.01 g; 5 mmol) in DMF (4.5 mL). The solution is stirred at T=0°C for 30 min; (4-aminophenyl)-trimethylammonium iodide hydrochloride (1.433g; 4.56 mmol) is then added to the mixture. N,N-dicyclohexylcarbodiimmide (1.02 g; 4.95 mmol) is added gradually in small portions. After stirring at T=0°C for 2 h., the mixture is left to warm to r.t. Then it is stirred for 24 h. The DCU which is formed is filtered off and DMF is distilled off under reduced pressure. The residue is dissolved in H_2O and stirred in diisopropyl ether (30 mL) overnight at room temperature; the precipitate formed is filtered under vacuum and dried in oven at T=40°C for 6 h, yielding a white solid (1.67 g; 3.58 mmol);

$[\alpha]_D$ = -31 (c=1; CH_3OH)

^{1}H-NMR (DMSO-d_6): δ 7.85 (dd, 1H, J_1=8.4Hz, J_2=2Hz); 7.62 (d, 1H, J=2Hz); 7.24 (m, 2H); 7.10 (m, 2H); 7.02 (d, 2H, J=8.4Hz); 6.15 (bs, 1H, CONH); 3.50 (m, 1H); 3.25 (s, 9H); 2.45 (d, 2H, J=7Hz); 1.85 (m, 1H); 1.52 (d, 3H, J=7Hz); 0.90 (d, 6H, J=7Hz).

CLAIMS

1. (R)-2-aryl-propionamide compounds of formula (I):

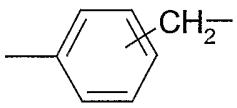


(I)

wherein

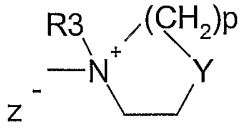
- Ar represents a substituted or non-substituted aryl group;
- R represents hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, optionally substituted by a CO_2R_4 group, wherein R_4 represents hydrogen or a linear or branched C_1-C_6 alkyl group or a linear or branched C_2-C_6 alkenyl group;
- X represents:

  linear or branched C_1-C_6 alkylene, C_4-C_6 alkenylene, C_4-C_6 alkynylene, optionally substituted by a CO_2R_4 group or by a $CONHR_5$ group wherein R_5 represents hydrogen, linear or branched C_2-C_6 alkyl or an OR_4 group, R_4 being defined as above;
- phenyl or a phenylmethylene group of formula:



- a $(CH_2)_m$-B-$(CH_2)_n$, group, optionally substituted by a CO_2R_4 or $CONHR_5$ group, as defined above, wherein B is an oxygen or sulfur atom, m is zero or an integer from 2 to 3 and n is an integer from 2 to 3; or B is a CO, SO or CONH group, m is an integer from 1 to 3 and n is an integer from 2 to 3;
- or X together with the nitrogen atom to which it is bound and with the R_1 group forms a nitrogen containing 3-7 membered heterocyclic monocyclic or polycyclic ring;
- R_1, R_2 and R_3 are independently linear or branched C_1-C_6 alkyl, optionally substituted by an oxygen or sulfur atom, a C_3-C_7 cycloalkyl, C_3-C_6 alkenyl, C_3-C_6-alkynyl, aryl, aryl-C_1-C_3-alkyl, hydroxy-C_2-C_3-alkyl group;

or R_1 and R_2 together with the N atom to which they are bound, form a nitrogen containing 3-7 membered heterocyclic ring of formula (II) and R_3 independently has the meanings as defined above,



(II)

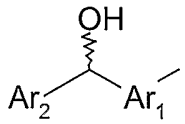
wherein Y represents a single bond, a methylene group, an oxygen atom, a nitrogen atom or a sulfur atom and p represents an integer from 0 to 3;

Z^- represents a pharmaceutically acceptable counter-ion of quaternary ammonium salts.

2. Compounds according to Claim1, wherein Ar is selected from

a) an Ar_a mono- or poly-substituted aryl group of (±) 2-aryl-propionic acids selected in the group consisting of alminoprofen, benoxaprofen, carprofen, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, loxoprofen, R-naproxen, pirprofen and its dehydro and dihydro derivatives, pranoprofen, surprofen, tiaprofenic acid, zaltoprofen;

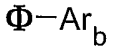
b) an aryl-hydroxymethyl-aryl group of formula (IIIa) both as diastereoisomer mixture, or as single diastereoisomers,



(IIIa)

wherein, when Ar_2 is phenyl Ar_1 is selected from the group consisting of phenyl and thien-2-yl while when Ar_1 is phenyl, Ar_2 is selected from the group consisting of phenyl, 4-thienyl, pyridyl.

c) an aryl of formula (IIIb):

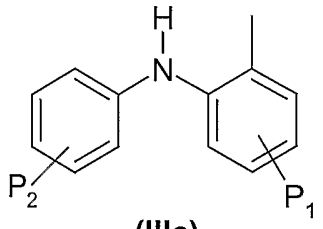


(IIIb)

wherein:

- Ar_b is a phenyl mono- or poly-substituted by hydroxy, mercapto, C_1-C_3-alcoxy, C_1-C_3-alkylthio, chlorine, fluorine, trifluoromethyl, nitro, amino, optionally substituted C_1-C_7-acylamino;
- Φ is hydrogen; a linear or branched C_1-C_5 alkyl, C_2-C_5- alkenyl or C_2-C_5-alkynyl residue optionally substituted by C_1-C_3-alkoxycarbonyl, substituted or non-substituted phenyl, 2-, 3- or 4-pyridyl, quinolin-2-yl; a C_3-C_6-cycloalkyl; 2-furyl; 3-tetrahydrofuryl; 2-thiophenyl; 2-tetrahydrothiophenyl or a a C_1-C_8-(alkanoyl, cycloalkanoyl, arylalkanoyl)-C_1-C_5- alkylamino group e.g. acetyl-N-methyl-amino, pivaloyl-N-ethyl-amino;

d) a 2-(phenylamino)-phenyl of formula (III c):



(IIIc)

wherein the substituents P_1 and P_2 indicate that the two phenyl groups bear, each independently, mono- or poly-substitutions with C_1-C_4-alkyl, C_1-C_3-alcoxy groups, chlorine, fluorine and/or trifluoromethyl.

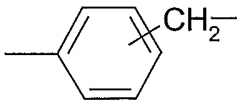
3. Compounds according to any of the previous Claims wherein:

R is hydrogen;

X is:

- a linear C_1-C_6 alkylene, preferably C_2-C_4, optionally substituted at C_1 by a $-CO_2R_4$ group as defined above;
- a linear C_1-C_6 alkylene optionally substituted at C_1 by a $-CONHR_5$ group wherein R_5 is OH;
- 2-butynylene, cis-2-butenylene, trans-2-butenylene;
- 3-oxa-pentylene, 3-thio-pentylene, 3-oxa-hexylene, 3-thio-hexylene;
- $(CH_2)_m$-CO-NH-$(CH_2)_n$-wherein m and n are each independently an integer from 2 to 3;
- (CHR')-CONH-$(CH_2)_n$ wherein n is an integer from 2 to 3 and R' is a methyl, having absolute configuration R or S;

- a phenyl or phenylmethylene group of formula:



- or X, together with the N atom, form an azocycloaliphatic ring.

4. Compounds according to Claim 3, wherein X is a linear C_2-C_4 alkylene.

5. Compounds according to any of Claims 1 to 3 wherein $NR_1R_2R_3$ group represents a trimethylammonium, triethylammonium, N-methyl-N,N-diethylammonium, N-methyl-N,N-diisopropylammonium, N-cyclohexylmethyl-N,N-dimethylammonium, N-cyclopentylamino-N,N-dimethylammonium, N-methyl-1-piperidinium, N-ethyl-1-piperidinium, N-methyl-4-morpholinium, N-methyl-4 thiomorpholinium, N-benzyl-N,N-dimethylammonium, N-allyl-1-piperidinium, 4-oxy-N-methyl-piperidinium group or X together with the amine N to which it is bound and with the R_1 group, forms a nitrogen containing 5-6 membered heterocyclic ring and the substituents R_2 and R_3 represent independently a methyl or cyclohexyl residue.

6. Compounds according to any of Claims 1 to 5, wherein Ar is selected from 4-isobutylphenyl, 4-cyclohexylmethylphenyl, 4-(2-methyl)allyl-phenyl, 3-phenoxyphenyl, 3-benzoyl-phenyl, 3-acetyl-phenyl, the single (R) (S) diastereoisomers and the diastereoisomeric (R,S) mixture of 3-C_6H_5-CH(OH)-phenyl, 3-CH_3-CH(OH)-phenyl, 5-C_6H_5-CH(OH)-thienyl, 4-thienyl-CH(OH)-phenyl, 3-(pyrid-3-yl)-CH(OH)-phenyl, 5-benzoyl-thien-2-yl, 4-thienoyl-phenyl, 3-nicotinoyl-phenyl, 2-fluoro-4-phenyl, 6-metoxy-2-naphthyl, 5-benzoyl-2-acetoxy-phenyl, 5-benzoyl-2-hydroxy-phenyl, 4-cyclopentyl-phenyl, 4-(2-oxo-cyclopentyl)-phenyl, 4-(2-oxo-cyclohexyl)-phenyl.

7. Compounds according to Claims 1 or 5, wherein Ar is a phenyl group 3-substituted by isoprop-1-en-1-yl-isopropyl, pent-2-en-3-yl, pent-3-yl; 1-phenylethylen-1-yl; α-methylbenzyl.

8. Compounds according to Claim 1 or 5, wherein the Ar groups in the formula (IIIc) are 2-(2,6-dichloro-phenyl-amino)-phenyl; 2-(2,6-dichlorophenyl-amino)-5-

chloro-phenyl; 2-(2,6-dichloro-3-methyl-phenyl-amino)-phenyl; 2-(3-trifluoromethyl-phenylamino)-phenyl.

9. Compounds according to any one of the previous Claims, wherein Z^- is a halide chosen from Cl^-, I^-, Br^-, a sulfate anion, methanesulfonate or p-toluenesulfonate.

10. Compounds according to any one of the previous Claims, selected from:

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-trimethylammonium iodide;

(R)-{3-[2-(3-benzoylphenyl)-propionylamino] propyl}-trimethylammonium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl} -N-ethyl-N,N-dimethylammonium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-N-cyclohexylmethyl- N,N-dimethylammonium iodide;

(R)-{3-[2-(4-cyclopentylmethylphenyl)-propionylamino] propyl}-trimethylammonium iodide;

(R)-{3-[2-(3-benzoylphenyl)-propionylamino] propyl}-N-isopropyl-N,N-dimethylammonium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] butyl-trimethylammonium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-1-methyl-piperidinium iodide;

(R)-{3-[2-(3-benzoylphenyl)-propionylamino] propyl}-1-methyl piperidinium iodide;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] propyl}-4-methyl-morpholinium iodide;

(R)-{3-[2-(3-isopropylphenyl)-propionylamino] propyl}-4-methyl-thiomorpholinium methanesulfonate;

(R)-{3-[2-(4-isobutylphenyl)-propionylamino] ethyl-trimethylammonium bromide;

(R)-2-[(4-isobutylphenyl)-propionylamino]-1,1-dimethyl)piperidinium p-toluenesulfonate;

(R),(S')-2-(4-isobutylphenyl)-N-[(1-carboxy-2"-N,N,N-trimethylammonium)ethyl] propionamide methanesulfonate;

R(-)-2-[(4-isobutylphenyl)-N-(trimethylammoniumethyl) methylamide] propionamide iodide;

(R)(3-{2-[2(2,6-dichlorophenylamino)-phenyl]-propionylamino}-propyl)-trimethylammonium methanesulfonate;

(2R), (4"S)1-{4-carboxy-4-[2-(4-isobutyl-phenyl)-propionylamino] butyl}-1-methyl-piperidinium iodide;

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(N-benzyl)-N,N-dimethylammonium iodide;

2R-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(1"methyl-4" carboxyamide) piperidinium iodide;

(2R)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-(1"-methyl-4" carbonyl) piperidinium iodide;

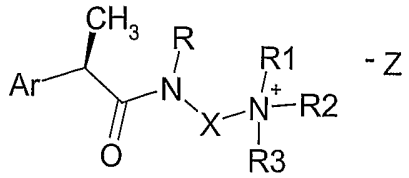
R(-)-{3,-[-(4'-isobutylphenyl)-propionylamino]-propyl}-triethylammonium iodide;

R(-)-{3-[2-(4'-isobutylphenyl)-propionylamino]-propyl}-1-allylpiperidinium bromide;

R(-)-2-[(4'-isobutyl)phenyl]-N-[4"-N,N,N-trimethylaminophenyl] propionamide iodide;

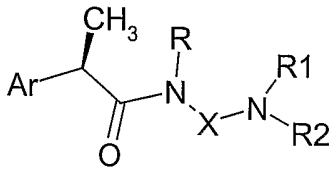
R(-)-2-[(4'-isobutyl)phenyl]-N-[4"-N,N,N-trimethylaminomethylphenyl] propionamide iodide.

11. Compounds according to any of Claims 1 to 10, for use as medicaments.
12. Compounds according to any of Claims 1 to 10, for use as inhibitors of the chemotaxis of neutrophils and monocytes induced by C5a.
13. Compounds according to any of Claims 1 to 10, for use in the treatment of psoriasis, pemphigus and pemphigoid, rheumatoid arthritis, intestinal chronic inflammatory pathologies including ulcerative colitis, acute respiratory distress syndrome, idiopathic fibrosis, cystic fibrosis, chronic obstructive pulmonary disease and glomerulonephritis.
14. Compounds according to any of Claims 1 to 10, for use in the prevention and the treatment of injury caused by ischemia and reperfusion.
15. Pharmaceutical compositions containing a compound according to Claims 1-10 in admixture with a suitable carrier thereof.
16. Process for the preparation of (R)-2-aryl-propionamide compounds of formula (I):



(I)

wherein Ar, X, R_1 ,R_2 ,R_3 have the meaning as defined in claim 1, comprising reaction of amides of formula (IV)



(IV)

with compounds of formula R_3Z, wherein Z is a conventional leaving group such as chloride, bromide, iodide, methanesulfonate, p-toluensulfonate, sulfate.

17. Amides of (R)-2-arylpropionic acids chosen from:

R(-)-2-[(3'-benzoyl)phenyl]-N-[3"-(N',N'-dimethylamino)propyl] propionamide

R(-)-2-[(3'-benzoyl)phenyl]-N-(3"-N"-piperidinepropyl) propionamide

R(-)-2-[(4'-Isobutyl)phenyl]-N-[3"-N'-(4",4-piperidinediol)propyl] propionamide

R(-)-2-[(4'-isobutyl)phenyl]-N-[3"-N'-(4"-carboxyamidepiperidine)propyl] propionamide

R(-)-2-[(4'-isobutyl)phenyl]-N-[4'-N,N-dimethylaminomethylphenyl] propionamide

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/10746

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C233/40 A61K31/16 A61K31/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 068377 A (ALLEGRETTI MARCELLO ;CESTA MARIA CANDIDA (IT); COLOTTA FRANCESCO () 6 September 2002 (2002-09-06) cited in the application page 7, line 6 - line 16 page 39 -page 40; claims; example 19; table 1	17
X	FR 2 410 641 A (MENARINI SAS) 29 June 1979 (1979-06-29)	1-5,9, 11,15,16
Y	page 1, line 1 -page 2, line 7; claims 8-13,16,17	6,10, 12-14,17
Y	FR 1 593 024 A (ARIES ROBERT) 25 May 1970 (1970-05-25) claims 1,2	6-8,10, 12-14,17

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 January 2003	05/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Seelmann, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/10746

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 58852 A (ALLEGRETTI MARCELLO ;CESTA MARIA CANDIDA (IT); COLOTTA FRANCESCO () 16 August 2001 (2001-08-16) page 6, line 26 -page 7, line 6; claims 1-4,9,12-14; table 4 _____	6-8,10, 12-14,17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/10746

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-3 (partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-3 (partially)

Present claims 1-3 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds wherein A is a substituted phenyl group; R = H and X is an alkylene chain or forms with R1 a piperidino ring.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/10746

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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